

BMJ Open Dutch injection versus surgery trial in patients with carpal tunnel syndrome (DISTRICTS): protocol of a randomised controlled trial comparing two treatment strategies

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ABSTRACT

Introduction Carpal tunnel syndrome (CTS) is the most common peripheral neuropathy. The optimal treatment strategy is still unknown. The objective of the Dutch Injection versus Surgery Trial in patients with CTS (DISTRICTS) is to investigate if initial surgery of CTS results in a better clinical outcome and is more cost-effective when compared with initial treatment with corticosteroid injection.

Methods and analysis The DISTRICTS is an ongoing multicenter, open-label randomised controlled trial. Participants with CTS are randomised to treatment with surgery or with a corticosteroid injection. If needed, any additional treatments after this first treatment are allowed and these are not dictated by the study protocol. The primary outcome is the difference between the groups in the proportion of participants recovered at 18 months. Recovery is defined as having no or mild symptoms as measured with the 6-item carpal tunnel symptoms scale. Secondary outcome measurements are among others: time to recovery, hand function, patient satisfaction, quality of life, additional treatments, adverse events, and use of care and health-related costs.

Ethics and dissemination The study was approved by the Medical Ethical Committee of the Amsterdam University Medical Centers (study number 2017-171). Study results will be disseminated in peer-reviewed journals and conferences.

Trial registration number ISRCTN Registry: 13164336.

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common peripheral neuropathy and is characterised by paresthesia, pain, numbness and sometimes weakness of the affected hand. Corticosteroid injections and surgery are the most common treatment options for patients with CTS.^{1–6} Clinical studies suggest that a surgical intervention is more effective than a steroid injection for relieving symptoms of

Strengths and limitations of this study

- In patients with carpal tunnel syndrome, treatment strategies starting with surgery or with a corticosteroid injection are compared using long-term clinically relevant outcomes.
- Due to the multicenter nature of this study, the large number of patients included, and the opportunity for additional treatment beyond randomization, external validity is anticipated to be high.
- Contrast between study arms in long-term outcomes may be diminished by additional treatment beyond randomisation, depending on patient status as judged by the treating physician.
- If the clinical outcomes of both treatment strategies are equal, the cost-effectiveness analysis may show which treatment is preferable.
- Possible patient preferences for an initial treatment for CTS may prevent patients from participating in the trial, which may impede the inclusion rate.

CTS.^{3,5,7,8} However, many neurologists initiate treatment with a steroid injection, because they consider this very easy to perform and relatively safe. Also, it is possible that with a corticosteroid injection, the need for surgery is avoided. It remains unclear with which intervention CTS treatment should be initiated.⁶ The lack of comparative knowledge regarding the best treatment strategy for CTS is also reflected in considerable practice variation in the treatment of CTS worldwide.^{9,10} Due to this practice variation, it is likely that many of the patients with CTS receive suboptimal treatment, resulting in higher societal costs. The objective of this study is to compare the clinical effectiveness and cost-effectiveness of a treatment strategy starting

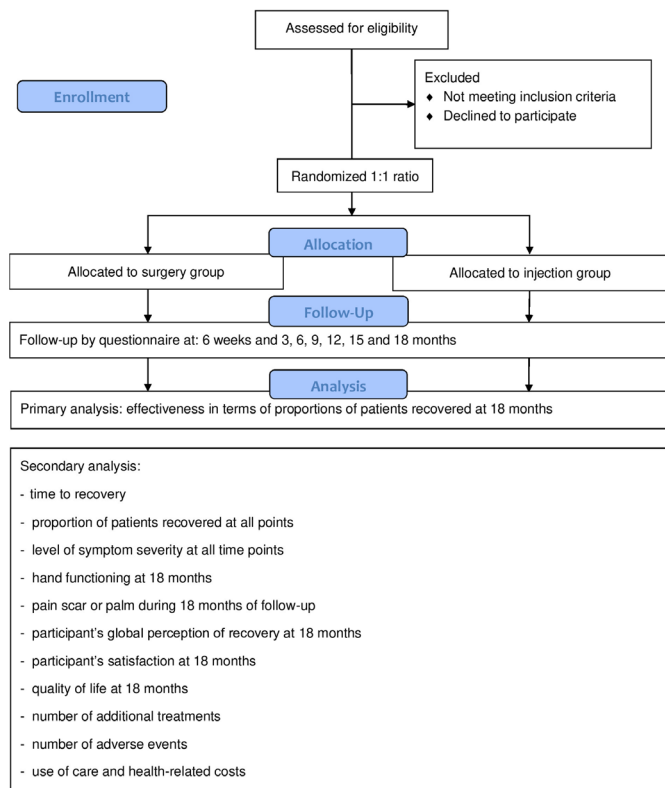


Figure 1 Study flow diagram.

with surgery compared with starting with a corticosteroid injection.

METHODS AND ANALYSIS

Study design

The Dutch Injection versus Surgery TRIal in patients with CTS (DISTRICTS) is an investigator-initiated, multi-center, open-label randomised controlled trial (RCT) with a follow-up of 18 months. Approximately 30 Dutch hospitals will be including participants. Data regarding baseline characteristics, treatment and follow-up assessments are collected according to a predefined protocol. Participants are randomised to the treatment strategy starting with surgery (surgery group) or to the treatment strategy starting with a corticosteroid injection (injection group). **Figure 1** shows the study flow diagram conform Consolidated Standards of Reporting Trials guidelines.

Study monitoring and data management are performed in accordance with the International Conference on Harmonisation—Good Clinical Practice guidelines by the Clinical Research Unit of the Amsterdam UMC, AMC. The DISTRICTS was registered at <http://www.controlled-trials.com> before start of the study.

The DISTRICTS started in December 2016 and is expected to end in June 2023.

Study participants

Inclusion criteria are: patients with clinically suspected CTS, which is confirmed by electrophysiological or sonographic testing and for which surgery and injection are

both potential treatment options. The symptoms of CTS have to be present for at least 6 weeks and treatment should be initiated within 6 weeks following inclusion. Participants have to be 18 years or older at time of examination. Patients can participate for the most affected hand only in case both hands are eligible. Exclusion criteria are: previous surgery for CTS on the ipsilateral wrist, an injection for CTS in the ipsilateral wrist less than 1 year ago, previous participation in the DISTRICTS, clinical or neurophysiological suggestion that the symptoms are due to another diagnosis, not able to comprehend Dutch self-report questionnaires, pregnancy, follow-up not possible, legally incompetent adults and no informed consent. Potential participants will be recruited from neurology outpatient clinics.

Different strategies to improve participant enrolment are used such as creating nationwide awareness of the DISTRICTS with a strong commitment of the Dutch Association of Neurology, regular and tailored contacts with participating centres, making expense allowance available and providing tools such as instruction videos to increase successful participant enrolment.

Recruitment of participants started in November 2017. We aim to finish inclusion in November 2021.

Patient and public involvement

Prior to starting the DISTRICTS, we invited the Netherlands Patients Federation to discuss the protocol and subsequently incorporated their advice. Because a Dutch patients society specific for CTS does not exist, further input was given by the Netherlands Repetitive Strain Injury society. No patients were involved in the recruitment and conduct of the study. Study participants will receive the results of the study by mail.

Study procedures and randomisation

After referral to the neurology outpatient clinics, potential participants will be informed about the study with an information letter. The local clinician evaluates a potential participant for eligibility. Subsequently, the clinician will verify if the potential participant is fully informed about the study and will discuss enrolment in the study. Informed consent is obtained (see DISTRICTS patient information and consent form; online supplemental file 1). Baseline and demographic characteristics, such as sex, length, weight, unilateral or bilateral CTS symptoms, duration of symptoms, severity of symptoms, associated underlying cause, previous corticosteroid injection for CTS in the ipsilateral wrist more than 1 year ago, are recorded, after which the participants will be randomised to either the surgery group or the injection group. In case a participant has bilateral CTS, the most affected hand will be included and treated in accordance with the study protocol. The preferred treatment and timing of treatment for the other hand is decided by the participant and the local clinician. If the symptoms in both hands are equally severe, the dominant hand will be included in the study. Participants will be randomised by the local

clinicians using a centralised web-based application (ALEA, <https://www.aleaclinical.eu>) in a 1:1 ratio stratified for (a) unilateral or bilateral CTS symptoms, (b) presence of a known associated underlying cause (yes/no) and (c) whether corticosteroid injection for CTS was given in the ipsilateral wrist more than 1 year ago (yes/no), using randomly permuted blocks with block sizes of 2, 4, 6 and 8.

Patients will be randomly assigned to two treatment strategies. One strategy consists of starting with a surgical treatment (surgery group). The other strategy consists of starting with a steroid injection proximal to the carpal tunnel (injection group). If needed, these treatments can be followed by any additional treatments within the 18 months of follow-up such as a second injection or surgical treatment. Independent of the initial treatment performed, patients will receive the usual care at the discretion of their physician.

Surgery group

A certified surgeon or a qualified resident will perform the surgical treatment. As we choose to stay as close as possible to daily practice, the participating centre will continue to refer the participating patients to their surgeon of choice, whether this be a neurosurgeon, plastic surgeon or other surgeon. Surgeons can use any proven surgical technique for decompression of the carpal tunnel. The surgeon describes the surgical technique in the surgical report form.

Injection group

A neurologist or other qualified staff member will administer the corticosteroid injection. As we choose to stay as close as possible to daily practice, participating centres will use their local protocol for injection, often based on the previous literature.³ Each participating centre is free in using their choice of brand and dosage of steroids, with or without local anaesthetic.

The use of analgesics is allowed. Additional treatments are allowed following the initial treatment at the participant and physician's discretion, and are not dictated by the protocol.

Baseline data collection is performed by local investigators. Participating centres send their report forms to the central data entry site. Follow-up questionnaires are sent 1 week before the upcoming follow-up timepoint. If the questionnaire is not returned within 2 weeks, a reminder and a new questionnaire will be sent. If there is no response within 1 week after the reminder, the patient will be contacted by telephone.

A central data manager performs and monitors data entry, and looks after timely questionnaire delivery. Data are checked for completeness. Patients will be contacted by telephone in case of missing data. In case of incomplete follow-up, effort is undertaken to collect the most relevant 18-month timepoint data. A separate data

management plan was made to secure correct data entry, coding and storage.

Sample size

The long-term effectiveness (12 months) of surgery is estimated to be approximately 75%²⁷ and the long-term effectiveness (12 months) of one to three injections, 38% to 61%.^{7,11} To our knowledge, there are scarce data available regarding the recovery rate in treatment strategies that may include combinations of different types of treatment at 18 months.

For the sample size calculation, we assume a recovery rate of 70% in the surgery group and 60% in the injection group. We consider this 10% difference in recovery rate the minimal clinically important difference. A Fisher's exact test with a 0.05 two-sided significance level will have 80% power to detect the difference between a proportion of 0.70 (recovery after initial surgery) and a proportion of 0.60 (recovery after initial corticosteroid injection) when the sample size in each group is 376 (752 participants in total). Anticipating a 20% attrition rate, we will include $(376/0.80 =)$ 470 participants per treatment group, which are 940 participants in total.

Outcome measures

The primary outcome is the proportion of participants recovered at 18 months. Recovery is defined as having no or mild symptoms; that is, a score of less than eight points on the 6-item carpal tunnel symptoms scale (CTS-6).¹² Secondary outcomes are: time to recovery during 18-month follow-up, proportion of participants recovered at all timepoints during 18-month follow-up, symptom severity at all timepoints during 18-month follow-up, upper limb functioning at 18 months measured using the QuickDASH,¹³ severity of pain in the scar/palm and pain-related activity limitation during 18-month follow-up using the palmar pain scale,¹⁴ participant's global perception of recovery at 18 months measured with a seven-point Likert-type item, participant's satisfaction at 18 months measured with a seven-point Likert-type item, health-related quality of life at 18 months assessed with the EuroQol 5-level EQ-5D (EQ-5D-5L),¹⁵ number and type of additional treatments during 18-month follow-up, adverse events during 18-month follow-up, use of care and health-related costs during follow-up assessed with an adapted version of the Medical Consumption Questionnaire (iMCQ) and the Productivity Cost Questionnaire (iPCQ).¹⁶ Data will be collected at baseline, 6 weeks and at 3, 6, 9, 12, 15 and 18 months (table 1). Baseline data are acquired during the visit at the neurology outpatient clinic. All other follow-up consists of participants completing self-report questionnaires, which are collected centrally.

Statistics

We will prepare an in-depth statistical analysis plan before the database is finalised, cleaned and locked. Briefly, the statistical analyses will be based on the

Table 1 Assessment schedule

	Inclusion	Baseline	6 weeks	3 months	6 months	9 months	12 months	15 months	18 months
Inclusion and exclusion criteria	x								
Baseline characteristics		x							
Symptom severity (CTS-6)		x	x	x	x	x	x	x	x
Upper limb functioning (QuickDash)		x							x
Pain palm/scar (palmar pain scale)			x	x	x	x	x	x	x
Perceived recovery (Likert-type)									x
Participant satisfaction (Likert-type)									x
Quality of life (EuroQol)		x							x
Additional treatment			x	x	x	x	x	x	x
Adverse events			x	x	x	x	x	x	x
Care use (iMCQ, iPCQ)				x	x	x	x	x	x

blank, no assessment; CTS-6, carpal tunnel symptoms scale; iMCQ, Medical Consumption Questionnaire; iPCQ, Productivity Cost Questionnaire; x, assessment.

intention-to-treat principle. Baseline patient characteristics will be summarised using descriptive statistics. The primary outcome, the between-group difference in the proportion of participants recovered at 18 months, will be analysed using the Fisher's exact test. Recovery at 18 months is defined as scoring less than eight points on the CTS-6.¹² Effect size will be expressed in a crude OR with its 95% CI. Additionally, the primary outcome will be analysed using logistic regression, including the three stratification variables into the model. Effect size will be expressed in an adjusted OR with corresponding 95% CI. Only in case of disbalance in baseline characteristics arisen by chance, we will perform further multivariable analyses with inclusion of potentially confounding variables, such as age, gender, duration of symptoms and severity of symptoms, to assess their effect on primary outcome. To assess the robustness of our findings, we will also perform a sensitivity analysis. In this analysis, a participant will be classified as having recovered if (s)he scores less than nine points on the total CTS-6 and less than three points on any individual item of the CTS-6. We will perform the same unadjusted analysis of the redefined primary outcome as described above.

Formal statistical tests will not be performed to examine differences between the secondary outcomes in the treatment groups. Differences between the surgery and injection groups with regard to the secondary outcomes measured at single timepoints will be summarised using appropriate parameters, such as hazard ratios (expressing the between-group difference in time to recovery) and proportions, means or medians and presented with their corresponding 95% CIs. Differences between the surgery and injection groups with respect to longitudinally measured outcomes will be analysed using a generalised linear mixed-effect model with treatment group as a fixed-effect and an appropriate random-effect structure.

A two-sided p value < 0.05 will be considered statistically significant. All statistical analyses will be performed in the current version of IBM SPSS Statistics for Windows (IBM Corp).

Economic evaluation

A prospective economic evaluation is set up alongside the trial, providing insight in the cumulative health-care costs, from a societal perspective, associated with 18-month follow-up. Cost categories and overall costs will be compared between both strategies and where relevant, differences will be calculated, inclusive of 95% CIs.

The economic evaluation is set-up as a cost-effectiveness analysis using the primary outcome measure (recovery as defined at 18-month follow-up) and a cost-utility analysis, with the costs per quality-adjusted life year (QALY) as the outcome. Utility will be measured using QALY values, derived from the EuroQol EQ-5D-5L. We will monitor the use of healthcare resources by the iMCQ tailored to patients with CTS. The iMCQ is used to measure the volumes of received care, for example, out-of-hospital consultations such as for general physician

and physiotherapist. Time off work and presenteeism will be obtained from the iPCQ. Both direct and indirect costs are included. Data will be collected at 3, 6, 12 and 18 months.

Differences between the interventions will be statistically evaluated with bias-corrected bootstrap analysis.¹⁷ Scenario analysis will be performed to extrapolate the consequences of implementation and concrete performance of both interventions in the pointed population. The validity of the developed scenarios will be studied in a sensitivity analysis varying cost estimates and probabilities.

We will extrapolate the outcomes of the economic evaluation using a budget impact analysis in accordance with the International Society for Pharmacoeconomics and Outcomes Research guidelines.¹⁸

DISCUSSION

This study compares the clinical effectiveness and cost-effectiveness of two treatments strategies in CTS, either starting with surgery or starting with a corticosteroid injection, but subsequently leaving additional treatment choices at the discretion of the patient and treating physician over a 1.5-year period.

In long-term follow-up (12 months), the effectiveness of surgery is estimated to be approximately 75%.²⁷ In short-term follow-up (1 month), the effectiveness of a single corticosteroid injection is estimated to be approximately 75%,³ while in long-term follow-up, this is estimated to be 25%–50%.^{38 11 19} In case of one to three subsequent injections, the long-term effectiveness could be 38%–61%.^{7 11} This is not only in line with a study that showed that after recurrence of CTS complaints, but also in case of unresponsiveness to a first injection, around 70% improved with a second corticosteroid injection.²⁰ Both treatments (ie, surgery and injection) differ regarding efficacy and side effects profile and their place relative to each other in the treatment of CTS is unknown. Potentially, a corticosteroid injection could postpone the benefit of a more effective treatment (ie, surgery), conversely a single injection or repeated injections could reduce the number of patients that require surgery.

Other treatments than corticosteroid injections and surgery are used for CTS, such as splints, laser therapy and ultrasound. Limited evidence showed that splints are more effective than no treatment in the short term,²¹ but a single corticosteroid injection showed superior clinical effectiveness at 6 weeks compared with night-resting splints in patients presenting in primary care.²² Still, splints can be used as treatment in specific circumstances, such as during pregnancy or patients with contraindications to surgery and corticosteroid injection. For all other CTS treatments, evidence is lacking.

It must be taken into consideration that our sample size is based on a 10% difference in recovery rate between both treatment strategies, which is considered the minimal clinically important difference. This assumption is based on expert opinion in conjunction with patient

representatives, because we could not retrieve a scientific underpinned threshold for the minimal clinically important difference in recovery rate in the literature.

To measure symptom severity and treatment outcome, we employed the CTS-6. The CTS-6 is an abbreviated and validated questionnaire derived from the Boston Carpal Tunnel Syndrome Questionnaire and highly responsive to change of symptoms.^{12 14} In the inclusion phase of the trial, a short scale diminishes the workload for the local clinician, thus increasing the chances that as many patients are included as possible, in the follow-up phase a short scale likely improves patient acceptance and increases the response rate.

The prospective economic evaluation will provide insight in the cumulative healthcare costs. These costs are expected to differ between the strategies, and important healthcare costs will be related to the improvement in recovery within the follow-up time from a societal perspective. A prospective study in primary care setting in England showed that corticosteroid injections were cost-effective over the use of night splints.²² A prospective study in neurological outpatient clinics in the Netherlands showed that initial surgery was more cost-effective than splinting.²³ A retrospective single-centre study in the USA showed no difference between the direct cost of nonsurgical care of CTS from that of surgical treatment without preoperative splinting or therapy; however, CTS surgery was associated with favourable incremental cost-utility ratio.²⁴ There are no prospective studies comparing cost-effectiveness of proposed long-term treatment strategies in CTS.

One of the inclusion criteria in our study is that surgery and injection are both considered as potential treatments for the CTS related symptoms. There is no evidence that symptom severity or the severity of abnormalities found with electrophysiological or sonographic studies clearly directs to either surgery or corticosteroid injection as initial treatment. Poor prognostic factors for recovery after corticosteroid injection might be duration of symptoms, positive Phalen's test and thenar wasting, although evidence was inconclusive.²⁵ There is no clear evidence that corticosteroid injections are not effective in severe CTS or that less severe CTS does not benefit from surgery. Other difficulties are that grading of severity of CTS is attempted based on electrophysiological criteria. These do not consider severity of symptoms and signs. No consensus about the most appropriate grading system has been reached.^{26 27} Furthermore, in ultrasound-confirmed patients with CTS, these data are not available.

To successfully complete the DISTRICTS, 940 participants have to be included. To date, more than 30 Dutch centres take part in realising this. Because the inclusion process is mostly performed during specialised and time-efficient carpal tunnel outpatient clinics, it will be a challenge for these centres to include this relatively large number of participants.

The trial design is unique for CTS being an open-label RCT with long-term follow-up and using validated



self-reported, patient relevant outcome measurements. The trial not just compares surgical decompression with one corticosteroid injection, but compares treatment strategies, which start with the initial, randomised, allocated treatment, followed by long-term clinical care as usual for 1.5 years. We did not blind for the initial allocated treatment (ie, initial treatment with surgery or injection) as we aim to compare treatment strategies and knowledge about the initial treatment could be essential for choosing a subsequent treatment. Also, blinding of patients with dummy surgery is not considered ethical in this context.

With regard to outcome assessment, we chose for validated self-reported, patient relevant outcome measurements. Arguments to choose for these patient relevant outcome measures are that in CTS care, symptom perception is the most important determinant to seek treatment and also to determine treatment effectiveness. The self-report questionnaires allow the participant to report their symptoms, prevents hospital visits just for study reasons and minimise the time investment for clinicians. These questionnaires also include (serious) adverse events and additional care use. It should be taken into account that participants might report adverse events differently than clinicians. We considered secondary outcome measures such as sensory signs, strength, and neurophysiological and ultrasound measures, but none of these outcomes showed convincing evidence of being useful in addition,^{28–30} while additional hospital visits and standardised assessments would be mandatory. Due to the open-label design, we are aware of the risk of bias in collecting unblinded endpoint measurements. Still, a prospective randomised open, blinded endpoint design was not chosen as a blinded physician assessing the outcomes would still need to ask the patient for symptom perception. An additional advantage of focusing patient relevant outcome measures based on self-reporting is that it may increase external validity of the results.

This study is innovative in the way it finally compares the clinical effectiveness and costs-effectiveness of two treatment strategies that have been daily clinical practice for years. The study results will have the potential to change the current CTS treatment strategies.

Ethics and dissemination

The DISTRICTS was approved by the Medical Ethical Committee of the Amsterdam University Medical Centers (study number 2017-171). The DISTRICTS is conducted according to the principles of the Declaration of Helsinki (version of 2013) and in accordance with the World Medical Association and other guidelines, regulations and acts. Study results will be disseminated in peer-reviewed journals and conferences. The study results will have the potential to change CTS treatment strategies.

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